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Should Azithromycin 1g be abandoned as a treatment for bacterial sexually transmitted infections? The case for and against.

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Running Title: Azithromycin 1g use and bacterial STI treatment

Where did it all go wrong? Azithromycin, a second generation macrolide antimicrobial, has been demonstrated to be highly efficacious both in vitro (low minimum inhibitory concentration (MIC) and in vivo against the common bacterial sexually transmitted infections *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Mycoplasma genitalium* (MG) and has good treponemicidal activity in animal studies.^{1,2} W1 2015 CDC guidelines, W2 European guideline Syphilis What's more its long half-life particularly intracellularly enabled it to be administered as single dose directly observed therapy, the preferred dosing schedule for STIs where poor compliance, and thus potential reduced efficacy, was considered a major concern with multidose regimens.³ Indeed its efficacy against chlamydia was considered to be so good a test of cure was not considered necessary.

I argue that the evidence indicates that azithromycin 1g is no longer at least 95% effective in achieving microbiological cure for bacterial STIs as recommended by WHO for first line treatment and therefore should not be used for treatment.⁴ In addition, as monotherapy, it is likely to be doing harm by inducing macrolide antimicrobial resistance. First, it is necessary to consider the mode of action and pharmacokinetics of azithromycin given as a 1 g stat regimen (Figure 1) and its mechanism of action; second, the mechanism of macrolide antimicrobial development and third, reappraise the evidence of efficacy in vivo against the common bacterial STIs, NG , syphilis, CT MG and non-gonococcal urethritis (NGU).

Azithromycin is a bacteriostatic antibiotic and duration of exposure to levels > MIC 90 are likely to be important in determining microbiological cure, particularly if the micro-organism is slow growing.^{5,6} Although there is limited evidence on the pharmacokinetics of azithromycin in genito-urinary tract secretions, it is not unreasonable to consider serum concentrations as a proxy for these. Thus 1g is present intracellularly for at least 10 days at an MIC >90% for chlamydia but probably only 6 days extracellularly for MG which replicates, slowly, both intracellularly and extracellularly (Figure 1).^{1,2,7} Due to the slow clearance of azithromycin surviving bacteria could potentially be exposed to sub-MIC levels for prolonged periods of time which may promote emergence of antimicrobial resistance.⁷

A single mutation in the 23S rRNA gene confers antimicrobial resistance to azithromycin.^{5 7} Spontaneous genomic mutations are constantly occurring in bacteria,, such that it is likely single nucleotide changes that confer high-level antimicrobial resistance would also be likely to be randomly present in bacterial populations prior to treatment – heteroresistance.^{5 8} Bacteria hunt in packs and if you have one STI you are more likely to have another, which may not be apparent either because the infection is incubating and undetectable (syphilis), or is not detected because it has not been tested for. Thus treatment of one bacterial STI increases the risk of other bacterial STIs being exposed to azithromycin.

NG, utilising all known mechanisms of antimicrobial resistance, has developed antimicrobial resistance to all drugs previously and currently recommended for empirical monotherapy of gonorrhoea.⁹ (Azithromycin as monotherapy is not recommended and dual antimicrobial therapy is now the standard of care.^{9, W1} Indeed recently there was an outbreak of azithromycin resistance NG in the North of England.^{W3} Azithromycin antimicrobial resistance is now endemic in syphilis and azithromycin monotherapy as first line therapy is not recommended.^{W1, W2} Macrolide antimicrobial resistance can easily develop following exposure.^{W1, W2} A recent report from Shanghai, where 95% of isolates had macrolide antimicrobial resistance, suggested that the development of high levels of macrolide antimicrobial resistance may have at least partially been a consequence of exposure to azithromycin or erythromycin prescribed for other bacterial infections.¹⁰

Although Azithromycin 1g treatment of chlamydia in a recent meta-analysis was demonstrated to be 94% effective, this dropped to ~90% in men with chlamydia urethritis and <90% in rectal infection.¹¹ Recent evidence strongly suggests the majority of women with genito-urinary infection are co-infected in the rectum.¹²⁻¹⁴ Whether treatment failure from rectal infection with subsequent auto-inoculation of the genitourinary tract contributes to high re-infection rates in women at 3 months when treated with azithromycin 1g is unknown but theoretically possible.¹⁵

MG is an emerging sexually transmitted infection with a significant morbidity, causing NGU, cervicitis (notably post coital bleeding), probably PID and facilitates HIV transmission.^{2 16} As no diagnostic tests are widely available commercially, management is often syndromic using azithromycin 1 g.^{(W1}
^{W4)} Evidence is accumulating that not only is azithromycin 1g only 87% efficacious in wild type infection but that >10% of wild type infections develop macrolide antimicrobial resistance following treatment.^{5 17 18} In 2013 1.4 million CT infections were treated in the USA (<http://www.cdc.gov/std/stats13/chlamydia.htm>) of whom probably at least 3% were co-infected with MG, if 90% were treated with azithromycin and one assumes 12% developed antimicrobial resistance this would equate to production of 4500 separate macrolide resistant isolates, annually, which in turn would be transmissible.^{16 17} Taken together this could explain Lau et al observations that from 2009 the efficacy of azithromycin 1g has dropped from 87% to 67% and why MG macrolide antimicrobial resistance appears to be increasing over time and is now prevalent worldwide ranging from 20-100%.^{5 16 18}

In conclusion azithromycin as first line monotherapy is no longer recommended for NG and syphilis. Although recommended for chlamydia and NGU, not only may its efficacy in women be <95%, its widespread use for treating chlamydia, NGU and their contacts is probably driving the increasing prevalence of MG antimicrobial resistance. Currently only two widely available antimicrobials can effectively treat MG, second generation macrolides and moxifloxacin.⁵ Resistance to moxifloxacin is also emerging and it is therefore no surprise that dual macrolide and quinolone antimicrobial resistance isolates have been identified which are in effect untreatable with currently available antibiotics.⁵

In my opinion this is an excellent example of how mankind is managing to squander yet another precious resource. Azithromycin, a good antibiotic, can no longer be used for treating syphilis and this is likely to be the case for MG in the not too distant future. Commercial tests for MG will become more widely available from 2016 in Europe and 2017 in USA (personal communication Hologic). Continuing to use azithromycin 1g for the treatment of NGU and chlamydia with its advantages as

single dose directly observed therapy and being cheap is storing up problems which will become all too evident when testing for MG becomes clinically widely available.

The case against.

Azithromycin meets many of the criteria for the selection of drugs for the treatment of sexually transmitted infections as set out by the World Health Organisation.⁴ It has long been a stalwart of national and international guidelines for the treatment of bacterial STIs. However, the future of Azithromycin has been called into question with concerns over its efficacy and increasing macrolide resistance in several sexually transmitted organisms.¹⁹⁻²¹

STI treatment trials using Azithromycin focus predominantly on a 1 gram, single-dose regimen and, although some randomised controlled trials have been performed, the majority use observational study design. For uncomplicated uro-genital Chlamydia a cure rate of 94% is quoted in the metaanalysis by Kong but this is lower when limited to cure rates of symptomatic urethral and rectal chlamydia.^{11 19} Cure rates for *Mycoplasma genitalium* have steadily fallen over the years with countries reporting an increasing proportion of isolates as resistant to Azithromycin.¹⁸ A 2010 review of single dose Azithromycin, both 1 and 2 grams, for the treatment of gonorrhoea did find high cure rates but in an era of little documented macrolide resistance.²² All this has led to a general feeling of dissatisfaction with Azithromycin and many clinicians have started to favour the use of alternative antibiotics using non-single dose regimen, a move that is also reflected in some national guidelines.²³

Underlying this move away from stat doses in favour of more efficacious, multiple dose alternatives is the tacit understanding that we value efficacy more highly than single dose options. If this is true then why do we fixate on using 1g stat doses of Azithromycin in clinical trials? Are we not setting it up to fail when compared to multiple doses of alternative agents? Recent evidence suggests that five days of Azithromycin can effectively eradicate chlamydia with cure rates of 99%.²⁴ The consideration

of alternative dosing strategies when designing studies may help to push forward our understanding of how best to use Azithromycin and help to expand future treatment options.

However, several key factors associated with drug adherence may be of particular relevance in the treatment of STIs and actually favour the use of stat doses of Azithromycin. Patient factors such as younger age, smoking and alcohol use and stigma, fears and anger about the illness have been shown to reduce adherence. So too are several treatment-associated factors such as duration of treatment, frequency of dosing and requirement for storage.²⁵ Furthermore, the ability to use Azithromycin as a stat dose helped to facilitate the widespread rollout of the English National Chlamydia Screening Programme which targets sexually active men and women under the age of 25 years and to whom these key adherence factors are acutely relevant.²⁶

Although stable, transmitted and increasing levels of macrolide resistance is well documented in *Neisseria gonorrhoeae*, *Treponema pallidum* and *M. genitalium*, this is not the case in *Chlamydia trachomatis* with no single nucleotide polymorphisms associated with macrolide resistance having been identified in available isolates to date.⁶ In countries where large quantities of Azithromycin are used there has been no evidence of resistance in isolates from those who have failed treatment.^{27 28} On the other hand, stable and transmitted tetracycline resistance has been documented in *C. suis* (swine chlamydia) suggesting that a switch to doxycycline may not save us from significant resistance issues in the future.²⁹

Of course, there is no specific need to always use the same antibiotic for each case of an infection; an organism may be sensitive to multiple agents. This has been difficult to implement in practice for the treatment of STIs as information on the exact organism present and antimicrobial sensitivities may not be available immediately. However, this is changing with the expanding field of rapid point of care tests to detect both the organism and the presence of antimicrobial resistance. Moving forward it will be possible to individualise treatment in a way that has thus far eluded us.³⁰

The treatment of STIs in pregnancy is an area where Azithromycin has a key role. In particular, chlamydia is associated with numerous adverse sequelae in pregnancy.³¹⁻³³ Doxycycline is contraindicated in pregnancy and other alternatives to Azithromycin are not without significant disadvantages. Erythromycin is less than 95% effective and associated with significantly more side effects than Azithromycin with 19% of pregnant women discontinuing treatment in one study.³⁴ Amoxicillin has a better side effect profile and similar cure rates when compared to Erythromycin but, in vitro, can induce latency with the re-emergence of infection after treatment has ended causing concern.³⁵ Chlamydia is at least as common in young pregnant women as their non-pregnant counterparts and new evidence suggests that screening in antenatal clinics is likely cost-effective and possibly cost-saving in some situations.^{36,37}

Not everything about Azithromycin is perfect; no drug is. However, can we afford to throw the baby out with the bathwater when we have not fully explored the ways in which we can use Azithromycin? Investigating different dosing regimen and the use of cutting edge, rapid diagnostics for organisms and potential antimicrobial resistance will allow us to use Azithromycin in more intelligent ways. Furthermore, exploring combination therapies for the treatment of chlamydia and mycoplasma, as is already common place for gonorrhoea, may also be a useful direction of travel.⁵ We cannot abandon the use of Azithromycin for the treatment of bacterial STIs but it is right to question the way in which we currently use it.

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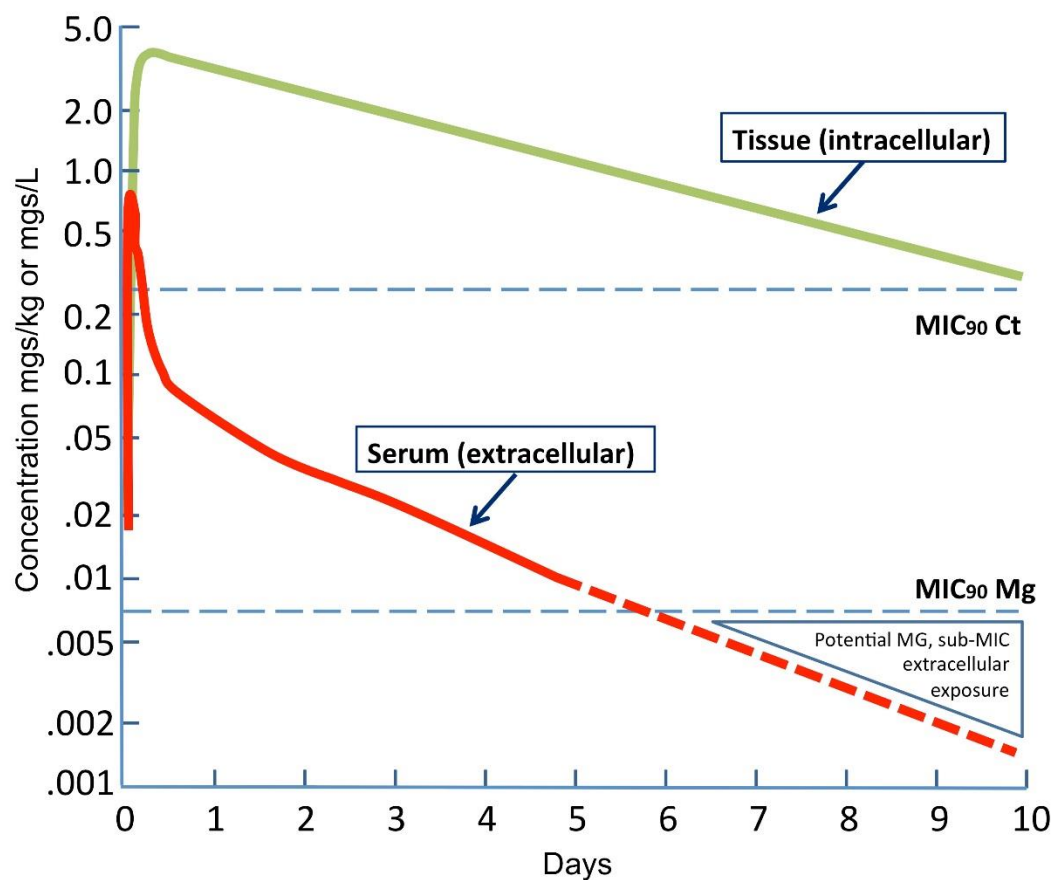


Figure 1

Figure 1 detailing anticipated serum and tissue concentrations after the administration of azithromycin 1g (adapted from Foulds et al.¹) and hypothetical change in serum concentration 5-10 days post administration. Courtesy of Mr Peter Greenhouse FRCOG

Supplementary on-line references

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